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Recent Innovation in Pretreatment for Skin Grafts Using Regenerative Medicine in the East

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1. Introduction

Chronic ulcers remain a significant health care concern today, especially in the elderly and immobile population. Pedicled or free flap transfers are usually applied to deep wounds in which bone and/or tendon are exposed. Despite improvements in reconstructive surgery techniques, operative invasion and complications, including flap necrosis and infection, are serious problems in patients whose general condition is unfavorable. For these patients, skin graft provides less invasive coverage of wounds as compared to the flap procedures. However, skin graft cannot survive on deep and poorly vascularized defects. Conversion of such defects to applicable beds to simple skin graft requires technologies to induce high-quality granulation tissue on compromised wounds. Stimulating the repair process after surgical debridement may achieve granulation tissue formation and shorten the period for skin grafts. For this purpose, regenerative medicine has attracted our attention. The characteristics of the methodology include the use of the three main tools of regenerative medicine; biomaterials, cytokines, and cells. This section introduces the technologies of regenerative medicine for wound bed preparation with particular focus on their progress in Asia.

All the patients illustrated in this chapter consented to the treatment. Clinical trials were approved by the Institutional Review Board (IRB) of Saitama Medical University.

2. Regenerative medicine for wound bed preparation

As already mentioned, the methodology includes the use of biomaterials, cytokines and cells, regenerative medicine's three main tools.

2.1 Biomaterials

Collagen is a natural substratum for various types of animal cells and is contained in tissues in large amounts as compared to other proteins (Linsenmayer, 1985). Advanced purification techniques can feasibly extract biocompatible and biodegenerative collagen matrix from

animal tissues. These properties support the collagen matrix as one of the most suitable components of artificial tissue substitutes for reconstruction of damaged tissues and organs (Chvapil et al., 1973; Doillon & Silver, 1986). Several types of collagen-based artificial skin have been reported since the initial description by Yannas and Burke (1980) (Leipziger et al., 1985; Doillon et al., 1986; Boyce et al., 1988; Bel et al., 1981).

In the West, Integra® (Siad Healthcare, Milano, Italy) has been generally used, and recently approved in Japan, but only for the treatment of burns. On the other hand, clinicians in Japan have widely used two types of artificial collagen matrix substitute dermis composed of an atelocollagen matrix (collagen matrix) with a silicone layer, namely TERUDERMIS (Terumo Corp, Tokyo, Japan) and Pelnac (Smith and Nephew Co., Ltd, Tokyo, Japan). These have been officially approved for the treatment of various skin defects caused by acute wounds as well as chronic wounds (Dantzer et al., 2001; Ichioka et al., 2003).

When these matrix substitutes are applied to a tissue defect, sprouting capillaries and fibroblasts migrate into the collagen, which acts as a scaffold for regeneration, resulting in induction of angiogenesis and fibroplasia. The autogenous regenerating tissue then gradually replaces the atelocollagen, and poorly vascularized deep defects are resurfaced by high-quality granulation tissue that can be easily covered with a simple skin graft (Ichioka et al., 2003). Collagen matrices have been reported to achieve less invasive reconstruction of severe defects with bone and/or tendon exposure that formerly required invasive tissue transfer (Braden & Bergstrom, 1989; Dantzer & Braye, 2001).

2.2 Cytokines

Cohen (1962) noticed that the purification of submaxillary gland extracts led to earlier eyelid separation and eruption of the incisor in mice, which eventually led to the isolation of the first growth factor as epidermal growth factor (EGF) as part of his Nobel Prize winning work. Since Cohen's discovery, it has been revealed that many growth factors are implicated in the processes of angiogenesis and wound healing (Greenhalgh, 1996; Stadelmann et al., 1998). In the chronic wound, the balance between stimulation and inhibition is destroyed (Stadelmann et al., 1998; Doughty & Sparks-Defriese, 2007) and fibroblasts have been reported to be less responsive to growth factors (Harding et al., 2002). The analysis of the supernatant from chronic pressure ulcers has shown decreased levels of growth factors, compared with the values in acute wound supernatant (Cooper et al., 1994). Deficiencies of growth factors in chronic ulcers suggest that the supplement of these factors might accelerate tissue repair processes. Therefore, growth factors have been proposed as therapeutic agents.

2.2.1 Cytokines for critical limb ischemia

Peripheral artery disease (PAD) is a major cause of the most difficult chronic limb ulcers. The occlusion of large limb arteries leads to ischemia, and can progress to critical limb ischemia (CLI). The treatment for ischemia is given priority in wound care. The main treatment strategy for severe, limb-threatening ischemia is either surgical or endovascular revascularization. If revascularization has failed or is not possible, major amputation is often inevitable. This relates to about 30% of all cases of severe limb ischemia (Adam et al., 2005). Regenerative medicine has been spotted as a new therapeutic option to induce angiogenesis. Recently gene therapies using cytokines have been developed as novel treatment strategies. The first in-human studies of gene therapy for the treatment of PAD and coronary artery

disease(CAD) were reported in the late 1990s (Isner et al., 1996; Schumacher et al., 1998; Laitinen et al., 1998). Since these initial reports, several gene therapies have been reported using growth factors, including vascular endothelial growth factor (VEGF) (Isner et al., 1996), fibroblast growth factor (FGF) (Nikol et al., 2008), hypoxia-inducible factor (HIF) (Rajagopalan et al., 2007), developmentally regulated endothelial locus (Del-1) (Grossman et al., 2007), and hepatocyte growth factor (HGF) (Powell et al., 2008). Among these studies, VEGF has been the most commonly employed approach. The beneficial effects of therapeutic angiogenesis using VEGF gene transfer have been reported in human patients with CLI and CAD (Isner et al., 1998; Baumgartner et al., 1998; Baumgartner et al., 2000; Losordo et al., 1998; Vale et al., 1999; Vale et al., 2000; Rosengart et al., 1999).

On the other hand, in Japan, Morishita et al (1999, 2002) have focused on HGF. HGF is also a potent angiogenic growth factor (Belle et al. 1998; Hayashi et al., 1999; Taniyama et al., 2001; Aoki et al., 2000), is a potent mitogen for a wide variety of cells and has angiogenic, antiapoptotic, and antifibrotic properties (Azuma et al., 2006; Matsumoto et al., 1996; Bussolino et al., 1992; Morishita et al., 2004). It is suggested that even in high-risk conditions for atherosclerosis, over expression of HGF is enough to stimulate collateral formation to treat ischemic symptoms (Taniyama et al., 2001). Furthermore, the mitogenic activity of HGF has been reported to be more potent than that of VEGF (Belle et al., 1998; Nakamura et al., 1996). Serum levels of HGF, but not VEGF, are elevated in CAD patients with collaterals, and elevated HGF levels are associated with better prognoses in patients with acute coronary syndromes (Lenihan et al., 2003; Heeschen et al., 2003). Morishita et al. (1999; 2004) conducted preclinical investigations and initial human safety studies of HGF gene therapy, which subsequently led to the phase II HGF-STAT trial. Patients with CLI were randomized to treatment with placebo or 1 of 3 doses of HGF plasmid (Powell et al., 2008). TcPO₂ was significantly more improved in patients who received the highest dose of HGF plasmid than in patients in whom a placebo or the lower HGF plasmid doses were administered. The authors concluded that intramuscular injection of HGF plasmid has an acceptable safety profile for the treatment of patients with CLI. Intramuscular injection of HGF plasmid may have a favorable effect on limb perfusion as measured by TcPO₂ in patients with CLI. Based on these findings, the phase III trial is now underway to determine whether HGF has a clinically meaningful effect on wound healing, limb salvage, and survival.

2.2.2 Cytokine products for topical application

Topical application of cytokines might be effective for wound healing. In the West, the growth factor product generally used is recombinant human platelet-derived growth factor (PDGF) (Regranex®). In South Korea, products based on PDGF, epidermal growth factor (EGF) (Easyef®) and basic fibroblast growth factor (bFGF) (Fibrast®) are available. In Japan, a bFGF product has been licensed since 2001 for use on various skin defects such as diabetic foot wounds, pressure ulcers, venous ulcers and trauma. The following subsections introduce EGF and bFGF for wound bed preparation.

2.2.2.1 Epidermal growth factor (EGF)

Epidermal growth factor (EGF) is a polypeptide of 53 amino acids that was first isolated from the mouse submaxillary gland by Cohen (1962) as previously mentioned. EGF acts by binding with the high affinity to epidermal growth factor receptor (EGFR) which is expressed in almost all types of tissue, triggering an increase in the expression of certain

genes that ultimately lead to DNA synthesis and cell proliferation (Herbst, 2004). EGF has been observed to stimulate the differentiation of epithelial cells, endothelial chemotaxis and angiogenesis, and fibroblast migration and proliferation, and to regulate extracellular matrix turnover (Deasy et al., 2002). Enhanced wound healing has been noted in dermal wounds treated with topical or subcutaneous EGF (Starkey et al., 1975). Franklin & Lynch (1979) recorded quicker epithelial regeneration and less scar contracture in EGF-treated wounds in rabbits.

With the introduction of recombinant human EGF in the 1980s, the range of studies increased to include burn wounds and chronic ulcers (Brown et al., 1989; Falanga et al., 1992). Studies with partial thickness human burn wounds and topical EGF confirmed a decrease in wound healing time (Brown et al., 1989). Although the use of EGF in human impaired wound healing by Falanga et al. (1992) showed a modest improvement in wound healing times and rate of epithelialization, the results were not statistically significant. Some other reports also suggested that the efficacy of EGF in chronic wounds is limited (Franklin & Lynch 1979; Brown et al., 1989). Therefore, no conclusions about the efficacy of EGF for chronic wounds can be made at present.

2.2.2.2 Basic fibroblast growth factor (bFGF)

In 1974, Gospodarowicz isolated a protein that accelerated the proliferation of fibroblasts from bovine pituitary glands and termed it the fibroblast growth factor (FGF) (Gospodarowicz et al., 1987; Gospodarowicz et al., 1988; Greenhalgh et al., 1990). One of the best-known FGF activities includes the stimulation of fibroblast proliferation leading to granulation tissue formation (Floss et al., 1997). FGF also plays a key role in proliferation of endothelial cells and keratinocytes and the mitogenesis of mesenchymal cells (Floss et al., 1997; Menetrey et al., 2000). Experimental studies have demonstrated that bFGF accelerates angiogenesis, granulation, and epithelialization (Gospodarowicz et al., 1988). Some clinical studies have shown the efficacy and safety of bFGF for the treatment of various wounds including diabetic ulcers, pressure ulcers and burns (Ishibashi et al., 1996; Ichioka et al., 2005).

2.3 Cell therapies

Stimulation of the microcirculation and enhancement of angiogenesis may promote granulation tissue formation on compromised wounds. For this purpose, several technologies using autologous cells have been developed. Bone marrow firstly attracted our attention as a possible beneficial material for wound healing, because it contains multipotential progenitor cells that can differentiate into endothelial cells and secrete several growth factors. Several reports have illustrated the potential of bone marrow to induce angiogenesis and also that it might contain early stem cells that can differentiate into non-hematopoietic tissues such as the skin (Ichioka et al., 2004; Yamaguchi et al., 2005). Asahara and colleagues (1999; 1997). have shown that vascular endothelial progenitor cells (EPCs), the population of mononuclear cells, from the bone marrow passed through the peripheral circulation and migrated locally to tumors, injured or ischemic regions. Furthermore, it has been suggested experimentally that bone marrow cells contribute to the formation of a matrix (Fathke et al., 2004; Badiavas et al., 2003), vascular formation (Asahara et al., 1999), secretion of angiogenic cytokines (Kamihata et al., 2001; Sanchez-Guijo et al., 2010), and stimulation of muscle cells. (Tateno et al., 2006.)

2.3.1 Cell therapies for critical limb ischemia

Several experiments have demonstrated therapeutic relevance of cell therapy for the ischemic limb. *Ex vivo*-expanded human EPCs transplanted into limb ischemia mice models showed a recovery of blood flow, an enhanced collateral density, and a 60% limb salvage (7% in controls) (Kalka et al., 2000). Iba et al. (2002) demonstrated that implantation of Peripheral blood mononuclear cells and platelets into ischemic limbs effectively induced collateral vessel formation using rat models, suggesting that this cell therapy is useful for therapeutic angiogenesis.

Some reports indicated the efficacy and feasibility of the clinical use of cell therapy (Tateishi-Yuyama et al., 2002; Kajiguchi et al., 2007; Matoba et al., 2008; Miyamoto et al., 2004). Therapeutic angiogenesis using cell transplantation (TACT) is a treatment strategy for non-option patients with CLI in Japan. Tateishi-Yuyama et al. (2002) reported the first large clinical study on the use of bone marrow derived mononuclear cells in the treatment of limb ischemia. According to this report, injection of bone marrow derived mononuclear cells into the muscle of the ischemic limb apparently improved the ankle-brachial index (ABI), transcutaneous oxygen pressure (TcPO₂), rest pain, and the pain free walking distance. The Japanese Ministry of Health, Labour and Welfare has approved this technology, namely "Therapeutic angiogenesis using bone marrow cell transplantation", as advanced medicine for critical limb ischemia. In addition, two other technologies using autologous cells, "Therapeutic angiogenesis using peripheral mononuclear cells" and "Therapeutic angiogenesis using peripheral blood stem cells", have been also approved (Matoba et al., 2008; Kajiguchi et al., 2007; Miyamoto et al., 2004).

2.3.2 Topical application of autologous cells

Topical application of bone marrow cells and platelet rich plasma (PRP) have been experimentally and clinically well-reported for their efficacy in the promotion of angiogenesis and wound healing (Wu et al., 2010; Lacci & Dardik, 2010).

2.3.2.1 Bone marrow

Bone marrow has long been known to participate in wound healing by providing inflammatory cells which produce cytokines and orchestrate a cascade of events (Gillitzer & Goebeler, 2001). Recent bodies of evidence suggest that bone marrow might also serve as a resource to provide skin progenitor cells (Krause et al., 2001; Liang & Bickenbach, 2002). Several reports have experimentally illustrated that topically applied bone marrow cells might promote wound healing (Badiavas et al., 2003; Sivan-Loukianova et al., 2003; McFarlin et al., 2006).

Badiavas et al. (2003) indicated that wounding stimulated the engraftment of bone marrow cells to the skin and induced bone marrow-derived cells to be incorporated and differentiate into non-hematopoietic skin structures using mice models. The authors concluded that bone marrow might be a valuable source of stem cells for the skin and possibly other organs. The application of peripheral blood mononuclear cells accelerated the neovascularization and epidermal healing in a model of chronic full-thickness skin wounds in diabetic mice (Sivan-Loukianova et al., 2003). McFarlin et al. (2006) found that local injection of mesenchymal stem cells significantly improved wound healing in an animal wound model. Bone marrow-derived cells have been reported as transit-amplifying cells in injured tissue where they differentiate into keratinocytes, using a mouse wound model (Borue et al., 2004).

Based on the results of the experimental studies, bone marrow-derived stem cells have been clinically used in the treatment of chronic wounds (Badiavas & Falanga, 2003; Ramsey et al.,

1999; Metcalfe & Ferguson, 2007). Badiavas & Falanga (2003) showed that topically applied autologous bone marrow-derived cells can bring about closure of long-standing and hard-to-heal wounds. These authors reported that bone marrow-derived cultured mesenchymal stem cells accelerated the healing of cutaneous wounds (Falanga et al., 2007). A similar clinical approach has been performed by Rogers et al (2008) and reported that topical application and injection into the wound periphery of bone marrow can be a useful and a potentially safe adjunct to wound simplification and ultimate closure (Rogers et al., 2008). It was reported that locally applied mononuclear bone marrow cells restored angiogenesis and promoted wound healing of an ulcer of the lower leg in a type 2 diabetic patient (Humpert et al., 2005).

In Japan, several methods of applying bone marrow derived cells for wound have also been tried. Mizuno et al. (2010) employed the combination of mononuclear bone marrow cells and allogeneic cultured dermal substitute for the treatment of intractable ulcers in critical limb ischemia. The authors injected mononuclear cells intramuscularly into the lower leg and around the wound area and applied allogeneic cultured dermal substitute on the wound surface (Mizuno et al., 2010). In our strategy, we impregnated autologous bone marrow cells into a collagen matrix (Terdermis): bone marrow-impregnated collagen matrix, (Fig.1) that has been utilized for the treatment of chronic wounds.

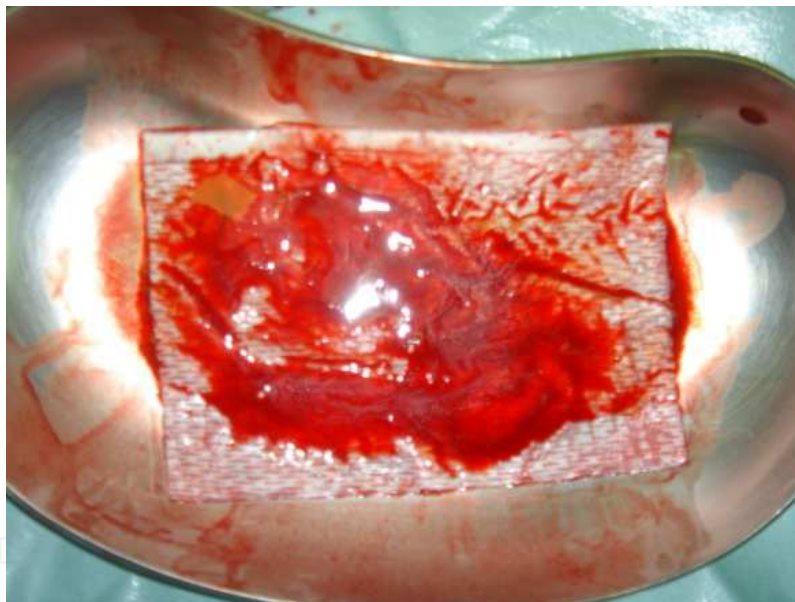


Fig. 1. The macroscopic finding of a bone marrow-impregnated collagen matrix

We have experimentally and clinically suggested the efficacy of this procedure for chronic ulcer treatment (Ichioka et al., 2005, 2009). One typical case is presented to illustrate the outcomes.

[patient 1] A 48-year-old woman suffered from a venous leg ulcer that had not healed despite seven years of standard conventional wound therapy (Fig. 2. A). Surgical debridement followed by bone marrow-impregnated collagen matrix application was undertaken under lumbar anesthesia (Fig. 2. B, C). Twenty-two days later, well-vascularized healthy granulation tissue had developed (Fig. 2. D), split-thickness skin graft was performed. The patient has remained free of complications for 29 months since treatment (Fig. 2. E).

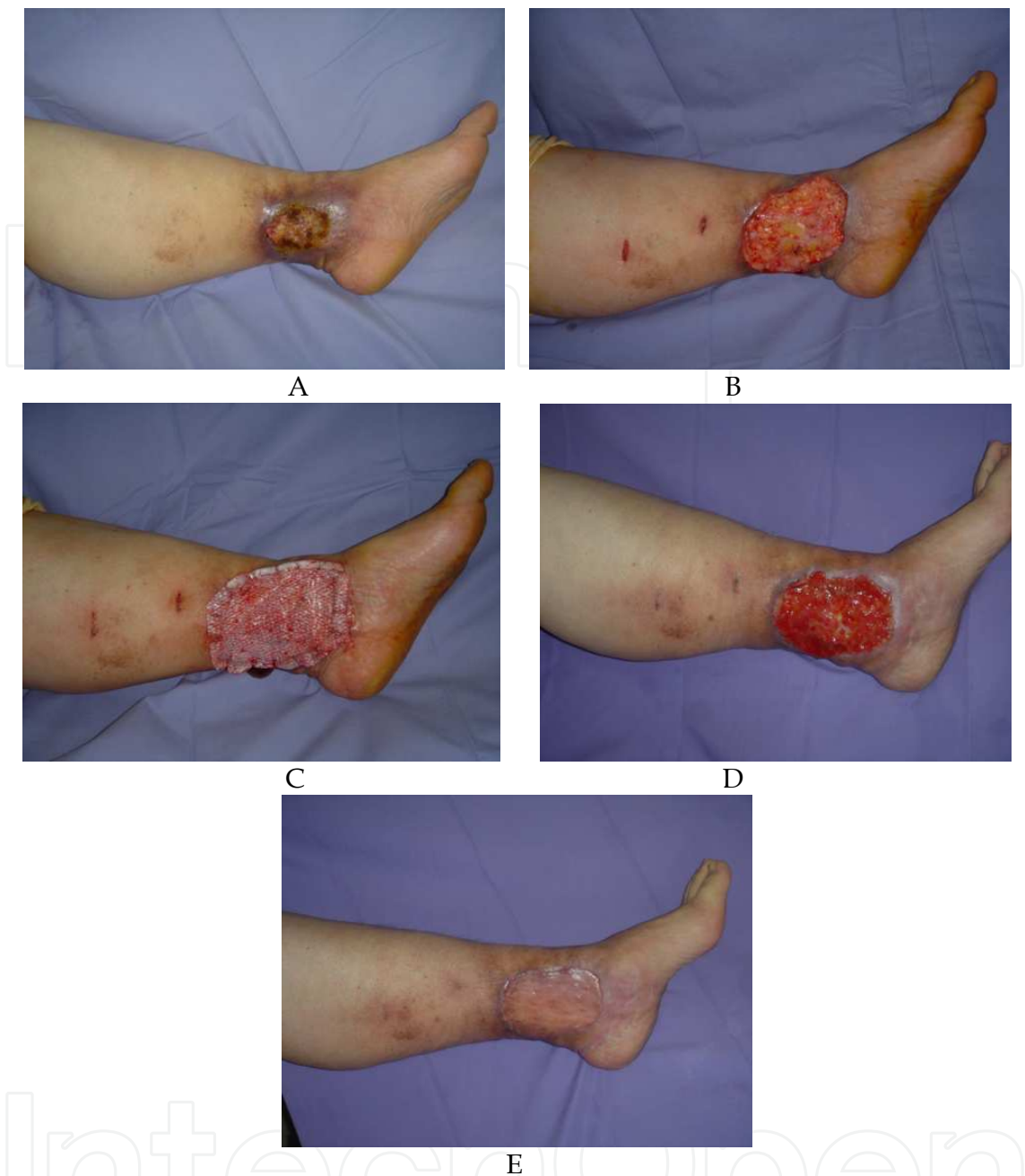


Fig. 2. (A) Nonhealing ulcer on the left lower limb before wound debridement. (B) Application of the bone marrow-impregnated collagen matrix after debridement. (C) Robust granulation tissue 3 weeks after PRP collagen application. (D) Split-thickness mesh skin grafting was performed. (E) Healed wound.

2.3.2.2 Platelet-rich plasma (PRP)

Besides the fundamental role in hemostatsis at the injured site, platelets initiate and enhance wound healing by releasing numerous plasma proteins and various growth factors (Everts et al., 2006; Knighton et al., 1986; Knighton et al., 1988). Platelets stimulate angiogenesis, proliferation and migration, and collagen synthesis. The main growth factors produced by platelets include platelet-derived growth factor (PDGF) (Bennett et al., 2003), transforming growth factor beta (TGF-β) (Assoian & Sporn., 1986), insulin-like growth factor (IGF-I)

(Hock et al., 1988), endothelial growth factor (EGF), vascular endothelial growth factor (VEGF) (Mohle et al., 1997), fibroblast growth factor (FGF) (Brunner et al., 1993). Platelet-rich plasma (PRP) is defined as a portion of the plasma fraction of autologous blood having a platelet concentration above baseline (Mehta & Watson, 2008; Marx, 2001). PRP can be supplied with a simple centrifugation procedure using solely autologous blood, suggesting that it is a minimally invasive method (Shashikiran et al., 2006; Bhanot & Alex, 2002). Roberts and Sporn (1993) and Marx (1998; 2001) have contributed a wealth of knowledge for the topical application of PRP in dentistry. In wound treatments, several investigations have reported the beneficial effects of PRP since its first report in 1985 (Driver et al., 2006). Margolis et al. (2001) reported a retrospective cohort study devised to estimate the effectiveness of platelet releasate (PR) in the treatment of diabetic neuropathic foot ulcers. The wounds of the 26,599 patients enrolled in this study, 43.1% of patients healed within 32 weeks, including 50% of patients treated with PRP and 41% of patients not treated with PR treatment. The investigators concluded that PRP was more effective than the standard care (Margolis et al., 2001). Driver et al. (2006) carried out the first prospective, randomized, controlled multicenter trial in the United States regarding the use of autologous PRP for the treatment of diabetic foot ulcers. The authors found the PRP treatment group attained significantly better outcomes as compared with the control group. (Driver et al., 2006). In our strategy, PRP is adapted with a collagen matrix to prepare the wound bed for skin graft or spontaneous closure (Fig. 3), and is applied to the debrided wound.



Fig. 3. Collagen matrix impregnated with PRP

Some recent studies have examined the clinical application of PRP using a drug delivery system (DDS). O'Connell et al. (2008) reported that a newly developed material containing PRP, which they named platelet-rich fibrin matrix membrane (PRFM), exhibited a gradual steady-state release of platelet-derived growth factors for as long as 7 days and potentially provided a fibrin scaffold to further facilitate the tissue repair process (O'Connell, et al. 2008). In Japan, Yazawa et al. (2003) reported that when a platelet concentrate was used in conjunction with fibrin glue as a carrier, the contents were released over a period of about 1 week. We have also reported that platelet-protein film (PPF) as an autologous fibrin clot which PRP and plasma proteins, might continuously release growth factors to the wound bed (Fig. 4) (Tanaka et al., 2007).

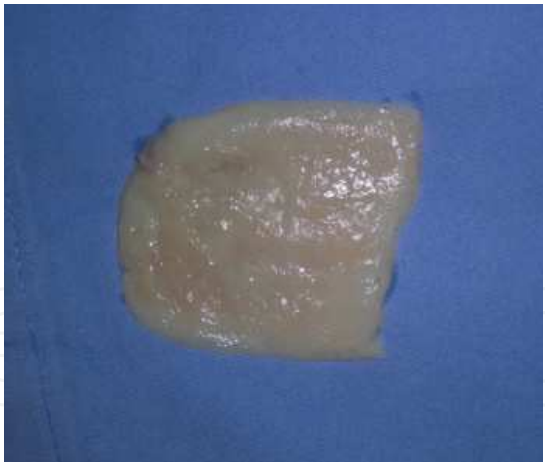


Fig. 4. The macroscopic finding of PRP

One successful case is presented to illustrate the possible outcome of treatment using PRP.
[Patient 1]
A 89-year-old female developed a pressure ulcer over the left lower limb; the ulcer had not healed despite three months of standard conventional wound therapy (Fig. 5 A). Surgical debridement followed by PRP collagen application was performed under general anesthesia (Fig. 5 B). Three weeks later, well-vascularized, healthy granulation tissue had developed (Fig. 5 C), and a split-thickness skin graft was performed to completely close the wound (Fig. 5 D). The patient has remained free of complications for 4 months since treatment (Fig. 5 E).



Fig. 5. (A) Nonhealing ulcer on the left lower limb before wound debridement.(B) Application of PRP collagen after debridement.(C) Good granulation tissue 3 weeks after PRP collagen application.(D) Split-thickness mesh skin graft was performed.(E) Healed wound.

3. Conclusion

Advanced regenerative medicine-based technologies currently provide successful and less invasive wound closure with spontaneous healing or can be used in combination with skin

grafting instead of invasive surgical tissue transfer. Recent developments in physical therapies including negative pressure wound therapy (NPWT) reinforce the efficacy of conservative wound treatment. However, we should always bear in mind that topical therapeutic management strategies work effectively only on adequately perfused wound beds under a moist environment without devitalized tissue or a critical bacterial burden.

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The procedure of skin grafting has been performed since 3000BC and with the aid of modern technology has evolved through the years. While the development of new techniques and devices has significantly improved the functional as well as the aesthetic results from skin grafting, the fundamentals of skin grafting have remained the same, a healthy vascular granulating wound bed free of infection. Adherence to the recipient bed is the most important factor in skin graft survival and research continues introducing new techniques that promote this process. Biological and synthetic skin substitutes have also provided better treatment options as well as HLA tissue typing and the use of growth factors. Even today, skin grafts remain the most common and least invasive procedure for the closure of soft tissue defects but the quest for perfection continues.

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